Background Microsatellite instability (MSI) tumors are characterized by defects in the DNA mismatch repair (MMR) genes that lead to the accumulation of mutations within microsatellite (MS) loci. Indels in MS regions of coding genes can result in the synthesis of shared frameshift peptide (FSP) neoantigens, expected to be immunogenic and safe. MSI tumors develop sporadically or secondary to hereditary predisposition as part of Lynch Syndrome (LS), one of the most common hereditary colorectal cancers. Nous-209 is a genetic vaccine encoding 209 neoantigens shared across sporadic and hereditary MSI tumors developed for interception and treatment of MSI tumors.1 A phase I trial (NCT04041310) combining theNous-209 vaccine with pembrolizumab anti-PD-1 antibody has been recently completed in metastatic colorectal, gastric and gastro-esophageal cancer patients showing excellent safety, immunogenicity, and promising signs of clinical efficacy.1,2 Here, we report the safety and immunogenicity of Nous-209 from the Phase Ib/II trial in LS carriers for the first 10 subjects.

Methods NCT05078866 is a Phase Ib/II single-arm, open-label, clinical trial testing Nous-209 monotherapy for immune-interception in LS carriers. Safety and immunogenicity are the co-primary objectives. Nous-209 is administered intramuscularly: one prime with a Great Ape Adenovirus (GAd20-209-FSPs) on day 1, and boost with a Modified Vaccinia Ankara (MVA-209-FSPs) at week 8. Blood samples are collected for biomarker assays (Baseline, weeks 3, 8, 9, 24, and 52). Immunogenicity is evaluated on PBMC before and after vaccination by ex-vivo IFNy ELISPOT assay.

Results On the data cutoff date (28 May 2023), 21 patients were enrolled in this NCI-sponsored study, 18 of those treated with both GAd and MVA. No dose limiting serious adverse events (SAEs) were observed (n=10), and the treatment appears safe and well tolerated. Immunogenicity was demonstrated in 100% of tested patients (n=10) with a mean peak response of ~700 IFNγ SFCs/mln PBMCs. No immune responses were detected at baseline prior vaccination in either previvors or survivors LS carriers. Nous-209-induced T cell responses were broad, recognizing different FSPs with induction of both CD4 and CD8 T cell responses. Deconvolution of T cell responses against predicted CD8 epitopes included in the FSPs pools showed multiple positive responses, confirming the optimal breadth of immune responses.

Conclusions Nous-209 is safe, well tolerated, and elicits potent and broad immune response in both LS carriers previvors and survivors, supporting Nous-209 development as a compelling approach for LS cancer interception.

REFERENCES

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